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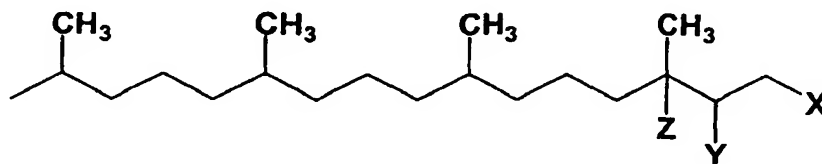
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(54) Title: **COMPOSITIONS FOR TREATING ACNE COMPRISING PHYTANDIOL AMINE**



(I)

(57) Abstract: The present invention relates to a phytandiol amine derivative represented by the following formula (I) and compositions for treating acne comprising the same: (I) wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

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**COMPOSITIONS FOR TREATING ACNE COMPRISING PHYTANDIOL AMINE****BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

5       The present invention relates to novel phytandiol amine derivatives and their use for treatment or prevention of acne. More particularly, the present invention relates to novel phytandiol amine derivatives and compositions for improving or alleviating acne comprising the above  
10 derivatives as active ingredient.

**DESCRIPTION OF THE RELATED ART**

Acne is inflammatory disease or disorder generally developed at sebum gland in hair follicle of skin, of  
15 which etiopathology, although unclear, is suggested as follows: Excess secretion of sebum triggered by testosterone, one of androgenic hormones, contributes to dyskeratinization of pilosebaceous canal, and in turn results in blockage in orifice for secretion of sebum,  
20 thereby accumulation of sebum in hair follicle. Excess accumulation of sebum is responsible for overgrowth of acne-causing bacteria, e.g. *Propionibacterium acnes*, in such follicle, and the lipase secreted from the bacteria hydrolyzes the accumulated sebum to form free fatty acids  
25 giving rise to inflammation through irritation of skin. Also, acne-causing bacteria, recognized as antigen, elicit immune reaction of individuals, resulting in inflammatory

reaction. In accordance with such mechanism, papule and inflammatory acne are developed, and when aggravated, wall of the follicle is disrupted and sequentially tissues are injured, finally leading to lesions of vesicular and  
5 pustule.

In an effort to inhibit generation and development of acne, a variety of pharmaceuticals formulated in the form of oral-administered drug or external preparation have been developed and employed. Such pharmaceuticals are: (a)  
10 anti-androgen agent for regulating secretion of androgenic hormones; (b) non-steroidal antiphlogostic agent exhibiting antinflammatory function; and (c) antimicrobial agents such as resorcinol, benzoyl peroxide, erythromycin and tetracycline to inhibit a growth of acne-causing  
15 bacteria. Recently, it is commonly employed to treat acne using retinoic acid and vitamin A derivatives.

Most of therapeutics for acne, however, is unfortunately suffered from adverse effects including inhibition of growth of epiderm, irritation or  
20 dyskeratinization of skin, resistance to antimicrobial agents and applicability.

Therefore, the use of low-irritating antimicrobial extracted from several plants has been recently attempted for controlling acne-causing bacteria in the field of  
25 cosmetics. Unfortunately, recent attempts as above-mentioned have recognized some drawbacks: (a) low antimicrobial activity and (b) inefficiency of separation

and purification of active ingredient from natural sources.

Under such circumstances, many researches have continuously focused on substances or compositions for treating acne disease or disorder with both better  
5 compatibility to human body and greater efficacy.

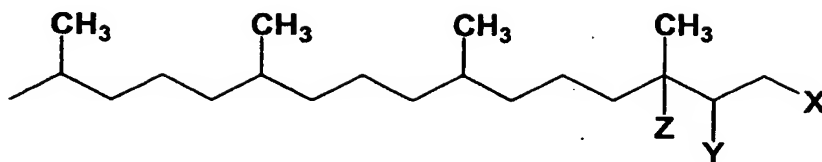
U.S. Patent No. 6,168,798 discloses non-irritating compositions for treating acne and other skin conditions comprising salicylic acid as active ingredient, and U.S. Patent No. 6,174,892 discloses a method of treating acne  
10 with 5-alpha reductase inhibitors such as finasteride.

In addition, U.S. Patent No. 4,775,663 suggests compositions for treating acne containing benzofuran derivatives and U.S. Patent No. 5,019,567 discloses benzoyl peroxide-quaternary ammonium lipophilic salicylate  
15 based pharmaceutical and cosmetic compositions and their use especially in treatment of acne.

Throughout this application, various patents are reference and citations are provided in parentheses. The disclosure of these patents in their entities are hereby  
20 incorporated by references into this application in order to more fully describe this invention and the state of the art to which this invention pertains.

#### SUMMARY OF THE INVENTION

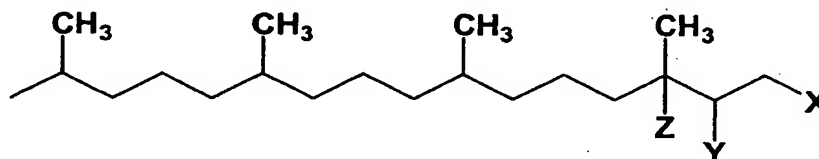
25 In one aspect of this invention, there is provided a phytandiol amine derivative represented by the following formula (I):



(I)

wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

In another aspect of this invention, there is provided a cosmetic composition for improving or alleviating acne, which comprises: (a) a cosmetically effective amount of phytandiol amine derivatives as active ingredient represented by the following formula (I); and (b) a cosmetically acceptable carrier,

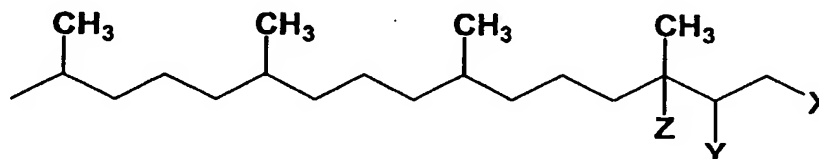


(I)

wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

In still another aspect of this invention, there is provided a pharmaceutical composition for treating or

preventing acne, which comprises: (a) a pharmaceutically effective amount of phytandiol amine derivatives as active ingredient represented by the following formula (I); and (b) a pharmaceutically acceptable carrier,



5

(I)

wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

10

Accordingly, it is an object of this invention to provide novel phytandiol amine derivatives.

It is another object of this invention to provide a cosmetic composition for improving or alleviating acne comprising the above derivatives as active ingredient.

It is still another object of this invention to provide a pharmaceutical composition for treating or preventing acne comprising the above derivatives as active ingredient.

20

Other objects and advantages of the present invention will become apparent from the detailed description to follow taken in conjugation with the appended claims.

**DETAILED DESCRIPTION OF THIS INVENTION**

The present invention is primarily directed to novel phytandiol amine derivatives. The derivatives have been prepared during the development of novel compounds highly effective in treating, alleviating or preventing certain skin disorders or diseases, generally called acne.

The phytandiol amine derivatives of this invention may be prepared from starting materials such as phytantriol and phytol, which is commercially available.

As known in formula (I), the phytandiol amine derivatives of this invention have amphiphilic property, thereby contributing to a good solubility in both aqueous solvent and non-aqueous solvent, as well as surface-activating property, and further exhibit high stability at high temperature, e.g., 90°C-100°C, and at a very wide range of pH. The above-described properties are responsible for a high workability in the formulation of cosmetic or pharmaceutical composition, especially, composition for topical application.

The phytandiol amine derivatives of this invention may be classified into three classes. The terms, "phytandiol amine derivative (I)" or "phytandiol amine (I)", used herein, refer to a derivative of formula (I) in which each of Y and Z is OH with the proviso that X is NH<sub>2</sub>. "Phytandiol amine derivative (II)" or "phytandiol amine (II)", as the terms are used herein, refer to a derivative of formula (I) in which each of X and Z is OH with the

proviso that Y is  $\text{NH}_2$ . The terms, "phytandiol amine derivative (III)" or "phytandiol amine (III)", used herein, refer to a derivative of formula (I) in which each of X and Y is OH with the proviso that Z is  $\text{NH}_2$ .

5

In the compositions of the present invention, the compounds represented by formula (I) employed as active ingredient, are very useful for treating, alleviating and preventing acne, and exhibit an anti-acne efficacy through the inhibition of growth of acne-causing pathogens like *Propionibacterium acnes* and *Propionibacterium avidum*. The compounds of formula (I) show very low Minimum Inhibitory Concentration (hereinafter referred to as "MIC") against acne-causing pathogens.

15 The term "acne", used herein, to which the present compositions are applied, includes all skin diseases or disorders generally called acne as well as all skin diseases or disorders which have a similar pathology to one of acne. For examples, the acne includes, but not limited to, acne aggregata, bromide acne, common acne, 20 conglobate acne, acne cosmetica, acne dtergicans, acne ephebica, acne fulminans, acne furunculoid, halogen acne, acne indurate, acne keloid, mechanical acne, acne medicamentosa, acne necrotica miliaris, acne neonatorum, 25 acne oil, acne papulosa, pomade acne, premenstrual acne, acne rosacea, acne sycosiformis, tropical acne, acne venenata, and acne vulgaris.



In the compositions of this invention, the amount of phytadiol amine derivatives is preferably in the range of 0.001-50 wt%, more preferably, 0.01-20 wt% and the most preferably, 0.05-5 wt%.

5       The cosmetic compositions of this invention may be formulated in a wide variety of form, for example, including a solution, a suspension, an emulsion, a paste, an ointment, a gel, a cream, a lotion, a powder, a soap, a surfactant-containing cleanser, an oil, a powder  
10 foundation, an emulsion foundation, a wax foundation and a spray.

      The cosmetically acceptable carrier contained in the present cosmetic composition, may be varied depending on the type of the formulation. For example, the formulation  
15 of ointment, pastes, creams or gels may comprise animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talc, zinc oxide or mixtures of these substances. In the formulation of powder or spray, it may  
20 comprise lactose, talc, silica, aluminum hydroxide, calcium silicate, polyamide powder and mixtures of these substances. Spray may additionally comprise the customary propellants, for example, chlorofluorohydrocarbons, propane/butane or dimethyl ether.

25       The formulation of solution and emulsion may comprise solvent, solubilizer and emulsifier, for example water, ethanol, isopropanol, ethyl carbonate, ethyl acetate,

benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylglycol, oils, in particular cottonseed oil, groundnut oil, maize germ oil, olive oil, castor oil and sesame seed oil, glycerol fatty esters, polyethylene glycol and fatty acid esters of sorbitan or mixtures of these substances. 5 The formulation of suspension may comprise liquid diluents, for example water, ethanol or propylene glycol, suspending agents, for example ethoxylated isosteary alcohols, polyoxyethylene sorbitol esters and poly oxyethylene sorbitan esters, micocrystalline cellulose, aluminum 10 metahydroxide, bentonite, agar and tragacanth or mixtures of these substances.

The formulation of soap may comprise alkali metal salts of fatty acids, salts of fatty acid hemiesters, fatty acid protein hydrolyzates, isethionates, lanolin, fatty alcohol, 15 vegetable oil, glycerol, sugars or mixtures of these substances.

Furthermore, the cosmetic compositions of this invention, may contain auxiliaries as well as carrier. The non-limiting examples of auxiliaries include preservatives, 20 antioxidants, stabilizers, solubilizers, vitamins, colorants, odor improvers or mixtures of these substances

In the pharmaceutical compositions of this invention, 25 the pharmaceutically acceptable carrier may be conventional one for formulation, including lactose,

dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium phosphate, alginate, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methyl cellulose, methylhydroxy benzoate, propylhydroxy benzoate, talc, stearic acid, magnesium and mineral oil, but not limited to. The pharmaceutical compositions of this invention, further may contain wetting agent, sweetening agent, emulsifying agent, suspending agent, preservatives, flavors, perfumes, lubricating agent, or mixtures of these substances.

The pharmaceutical compositions of this invention, may be administered orally or parenterally. The topical administration, especially topical application to skin, is the most preferable mode for the present compositions.

The correct dosage of the pharmaceutical compositions of this invention will vary according to the particular formulation, the mode of application, age, body weight and sex of the patient, diet, time of administration, condition of the patient, drug combinations, reaction sensitivities and severity of the disease. It is understood that the ordinary skilled physician will readily be able to determine and prescribe a correct dosage of this pharmaceutical compositions. An exemplary daily dosage unit for human host comprises an amount of from about 0.001 mg/kg to about 100 mg/kg.

According to the conventional techniques known to those

skilled in the art, the pharmaceutical compositions of this invention can be formulated with pharmaceutical acceptable carrier and/or vehicle as described above, finally providing several forms including a unit dosage  
5 form. Non-limiting examples of the formulations include, but not limited to, a solution, a suspension or an emulsion, an extract, an elixir, a powder, a granule, a tablet, a capsule, emplastra, a liniment, a lotion and an ointment.

10

The compositions of this invention are significantly effective in treating, alleviating and preventing acne without irritation and keratinization of skin and induction of resistance to antimicrobial agents even the  
15 case of a long-term application.

The following specific examples are intended to be illustrative of the invention and should not be construed as limiting the scope of the invention as defined by  
20 appended claims.

#### EXAMPLE

##### Example I: Preparation of Phytandiol Amine Derivative [I]

In a reactor 0.3 g of phytantriol (0.91 mmol) was  
25 dissolved in 20 ml of normal hexane and stirred for 10 min. at a room temperature, followed by addition of 0.21 g (1.09 mmol) of para-toluene sulfonylchloride. Following

the drop of the temperature of the reactor to 0°C, 0.11 g (1.09 mmol) of triethyl amine and a catalytic amount of pyridine were added dropwise and the temperature of the reactor was elevated to a room temperature, followed by stirring for 12 hr. Upon the completion of the reaction, the solvent was removed by distillation under reduced pressure. Then, 20 ml of chloroform was added to the concentrate for extraction and the extract was washed with saline. The washed extract was dried over anhydrous magnesium sulfate, followed by filtration and concentration to yield 0.48 g para-toluene sulfonyl phytandiol derivative as brown oil.

The yielded phytandiol derivative (0.48 g) was dissolved in 25 ml of dimethyl formamide and 0.06 g (1.00 mmol) of sodium azide was added, followed by reflux for 5 hr in order to substitute azide for para-toluene sulfonyl group. The reaction mixture was extracted with 50 ml of methylene chloride solution and washed with saline. Following drying over anhydrous magnesium sulfate, filtration and concentration, 0.29 g of azido phytandiol derivative was yielded.

In order to convert the azido phytandiol derivative to amine compound, 0.29 g of the yielded azido phytandiol (8.4 mmol) was subject to hydrogenation in ethyl alcohol with a catalytic amount of 10% palladium charcoal under 50 psi of hydrogen atmosphere for 3-4 hr, and finally 0.21 g of phytandiol amine derivative [I] (0.64 mmol) was

obtained in the form of yellow gel in the overall yield of 70%: Anal. Calcd. for  $C_{20}H_{43}NO_2$  (329.33): C 72.89; H 13.15; N 4.25; O 9.71; Found C 72.44; H 13.51; N 4.65; O 9.98

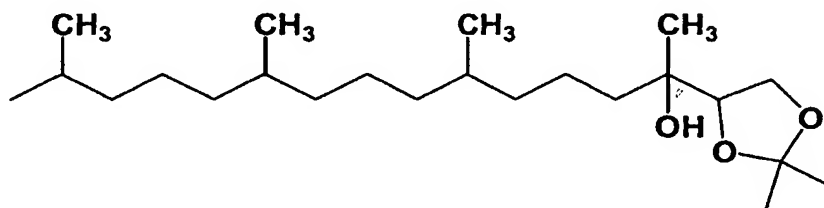
5 **Example II: Preparation of Phytandiol Amine Derivative [II]**

In a reactor 0.3 g of phytol (1.0 mmol) was dissolved in 30 ml of methylene chloride and then the temperature of the reactor was decreased to 0°C. While maintaining the temperature of the reactor, to the mixture was added 0.45 g of 77% chloroperoxy benzoic acid. After the completion of the reaction, the resultant was extracted with 50 ml of chloroform to prepare phytol derivative epoxidated at 2- and 3-positions. The phytol derivative was reacted with ammonia gas for 5 hr. to produce 0.21 g of phytandiol amine derivative [II] in the yield of 64%: Anal. Calcd. for  $C_{20}H_{43}NO_2$  (329.33): C 72.89; H 13.15; N 4.25; O 9.71; Found C 72.44; H 13.51; N 4.65; O 9.98

20 **Example III: Preparation of Phytandiol Amine Derivative [III]**

One g of phytantriol (3.0 mmol) was refluxed using deanstock apparatus for 15 hr in 25 ml of acetone solution with toluene sulfonic acid as catalyst. After the completion of the reaction, the acetone solvent was removed under reduced pressure and the resultant was extracted with chloroform solution. The extract was

washed with saturated sodium bicarbonate solution and was again washed with saline to obtain 0.3 g of (2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-6,10,14-trimethyl-pentadecan-2-ol) of which 1- and 2-positions were  
5 protected, which is represented by the following formula (IV):



(IV)

Thereafter, in 20 ml of normal hexane was dissolved 0.3 g of (2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-6,10,14-trimethyl-pentadecan-2-ol), and stirred for 10 min. at a  
10 room temperature, followed by addition of 0.18 g (0.97 mmol) of para-toluene sulfonylchloride. After the drop of the temperature of the reactor to 0°C, 3 equivalents of pyridine were added and the temperature of the reactor was  
15 elevated to a room temperature, followed by stirring for 12 hr. Upon the completion of the reaction, the solvent was removed by distillation under reduced pressure. Then, 20 ml of chloroform was added to the concentrate for extraction and the extract was washed with saline. The  
20 washed extract was dried over anhydrous magnesium sulfate, followed by filtration and concentration to yield 0.41 g of a compound substituted at 3-position with toluene sulfonyl in the form of yellow oil. In 20 ml of 2N HCl was

dissolved 0.41 g of the yellow oil, and then was reacted for 6 hr at 80°C to yield 0.21 g of 1,2-phytandiol derivative of which ring structure is cleaved.

The phytandiol derivative yielded (0.21 g) was dissolved  
5 in 25 ml of dimethyl formamide and 0.06 g (1.00 mmol) of sodium azide was added, followed by reflux for 5 hr to produce 0.15 g of phytandiol derivative substituted with azide. In order to reduce the azide-substituted phytandiol derivative to amine compound, 0.15 g of the azido  
10 phytandiol yielded was subject to hydrogenation in ethyl alcohol with a catalytic amount of 10% palladium charcoal under 50 psi of hydrogen atmosphere for 3-4 hr, and finally 0.20 g of phytandiol amine derivative [III] was obtained in the yield of 50%: Anal. Calcd. for  $C_{20}H_{43}NO_2$  (329.33):  
15 C 72.89; H 13.15; N 4.25; O 9.71; Found C 72.51; H 13.04; N 4.54; O 9.43

#### Example IV: Evaluation on Minimum Inhibitory Concentration

To evaluate an antimicrobial activity of the phytandiol  
20 amine of this invention against acne pathogen, the minimum inhibitory concentration (hereinafter referred to as "MIC") of the samples shown in Table 1 was measured as follows:

The sample to be tested was added to reinforced  
25 clostridial agar medium (available from Difco Co.) in the amount of 0.001-0.1%, followed by solidification of the medium. The suspension of acne pathogenic bacteria found



in Table 1 was streaked on the surface of the medium and the medium was incubated for 3 days at 35°C under anaerobic condition. The MIC was measured by the determination of the minimum concentration to completely inhibit the growth of the acne pathogenic bacteria, of which results are indicated in Table 1.

Table 1

Sample/Pathogen	<i>P. acnes</i> ATCC 6919	<i>P. acne</i> ATCC 11828	<i>P. avidum</i> ATCC 25577
Phytandiol amine[I]	0.002	0.002	0.002
Phytandiol amine[II]	0.002	0.002	0.002
Phytandiol amine[III]	0.003	0.004	0.003
Tea tree oil	1.0	0.2	1.0
Erythromycin	0.02	0.02	0.02
Chitosan	0.2	0.2	0.2
Benzoyl peroxide	0.1	0.1	0.1

As demonstrated in Table 1, the phytandiol amine derivatives of this invention represent antimicrobial activity against acne pathogens 10-50 times greater than erythromycin and benzoyl peroxide which are conventionally used as a therapeutic agent for acne.

Furthermore, the phytandiol amine derivatives of this invention are improved in terms of workability and skin-compatibility, thereby leading to little adverse effects. Therefore, the phytandiol amine derivatives of this invention can be excellent agents for treating acne and the compositions comprising the same are also expected to exhibit a remarkable treatment effect to acne.

**Example V: Evaluation on Antimicrobial Activity against  
Acne Pathogen of the Formulation Comprising the  
Present Compounds**

To elucidate antimicrobial activity against acne  
5 pathogens of the compositions comprising the phytandiol  
amine derivatives of this invention, a particular  
formulation of skin lotion as external application was  
prepared as the following Table 2. In Table 2, the amount  
of constituents is expressed in terms of wt%.

10 **Table 2**

Ingredients	Prep. 1	Prep. 2	Comp. Exam.
Phytandiol amine[I]	0.05	0.1	-
Glycerine	5.0	5.0	5.0
1,3-butylene glycol	3.0	3.0	3.0
PEG-1500	1.0	1.0	1.0
DL-panthenol	0.3	0.3	0.3
EDTA	0.02	0.02	0.02
Benzophenone-9	0.04	0.04	0.04
Sodium hyaluronate	5.0	5.0	5.0
Ethanol	10.0	10.0	10.0
Octyldodeces-16	0.2	0.2	0.2
Polysorbate 20	0.2	0.2	0.2
Allantoin	0.1	0.1	0.1
Preservative, perfume, colorant	Minute amount	minute amount	minute amount
Distilled water	Residual	Residual	residual
Total	100	100	100

The antimicrobial activities against acne-causing  
bacteria of the skin lotions of preparative examples 1 and  
2, and comparative example were measured as follows: The

acne-causing bacteria were cultured at 35°C under anaerobic condition, the colonies formed were taken with a platinum loop and were appropriately diluted by suspending in phosphate-buffered saline. 10 ml of reinforced clostridial agar medium were poured into each of plates and solidified, and then the diluted solution containing acne-causing bacteria was inoculated into each of the plates to the extent of 300-500 cfu. The plates were cultured in an anaerobic incubator and the number of colonies formed was counted, which is considered as the number of the original acne-causing bacteria ( $N_{ori}$ ).

The skin lotions of preparative examples 1 and 2, and comparative example were respectively mixed with reinforced clostridial agar medium to the extent of 10%, the acne-causing bacteria was inoculated into the mixture and cultured as above. The number of colonies formed is considered as the number of the final acne-causing bacteria ( $N_{fin}$ ). The antimicrobial activity against acne-causing bacteria was calculated in accordance with following equation, which is indicated in Table 3.

#### Equation

$$\text{Antimicrobial Activity(\%)} = [(N_{ori} - N_{fin}) / N_{ori}] \times 100$$

More than 90% of antimicrobial activity is evaluated as the possession of antimicrobial activity against acne-causing bacteria.

Table 3

Items	Prep. 1	Prep. 2	Comp. Exam.
No. of original acne-causing bacteria( $N_{ori}$ )	510	475	380
No. of final acne-causing bacteria ( $N_{fin}$ )	31	2	219
Antimicrobial activity against acne-causing bacteria(%)	93.9	99.5 >	42.3
Evaluation	adequate	adequate	inadequate

As found in Table 3, the formulations comprising the phytandiol amine derivative [I] of this invention exhibit antimicrobial activity against acne-causing bacteria much greater than the formulation without the derivative. In particular, the formulation containing 0.1 wt% of phytandiol amine derivative [I] approaches to 100% of antimicrobial activity.

While not shown in this specification, the formulations containing the phytandiol amine derivatives [II] or [III] of this invention give almost the same antimicrobial activity as one containing the phytandiol amine derivative [I]

Consequently, it is sure that the compositions comprising the phytandiol amine derivatives of this invention are highly effective in treating or preventing acne.

**Example VI: Evaluation on Improving or Alleviating Acne**

First, 60 women aged 17-29 years, who had acne symptom on their face, were randomly divided to three groups. The formulations of preparative examples 1 or 2, or comparative example were topically applied twice a day to three groups, respectively, for six weeks, in the morning and evening. The improving or alleviating effect for acne was assessed with the opinion from the tested women, which is indicated in Table 4.

10 **Table 4**

Time Period	Prep. 1	Prep. 2	Com. Exam.
1 week	±	±	±
2 weeks	+	+	±
3 weeks	+	++	±
4 weeks	++	+++	±
5 weeks	+++	+++	±
6 weeks	+++	+++	±

Note. +++: showing excellent improvement efficacy

++: showing significant improvement efficacy

+: showing slight improvement efficacy

±: not showing improvement efficacy but not showing  
aggravation efficacy

-: showing aggravation efficacy

As demonstrated in Table 4, the formulations of skin lotion containing phytandiol amine derivative [I] of this invention exhibit excellent improvement or alleviation effect on acne symptom, which appears explicitly from

about 3 weeks after application. Furthermore, the composition of this invention did not lead to irritation of skin, erythema and itch.

5

**FORMULATION EXAMPLE**

The following exemplified compositions were formulated according to conventional methods, which comprise the phytandiol amine [I] of this invention as active ingredient while the formulated compositions can be also applied to other phytandiol amine derivatives of this invention. Therefore, those skilled in the art will promptly recognize appropriate variations from the formulations both as to ingredients and as to the amount thereof.

15

**Formulation I**

Formulation I comprising the phytandiol amine [I] was prepared in the form of astringent cosmetic liquid, of which composition is found in Table 5.

20 **Table 5**

Ingredients	Amount (wt%)
Phytandiol amine [I]	0.1
Glycerine	2.0
1,3-butylene glycol	2.0
Allantoin	0.2
DL-panthenol	0.2
EDTA	0.02
Benzophenone-9	0.04
Sodium hyaluronate	3.0

Table 5-continued	
Ingredients	Amount (wt%)
Ethanol	15.0
Polysorbate 20	0.3
Preservative, perfume, colorant	Minute quantity
Distilled water	Residual quantity

**Formulation II**

Formulation II comprising the phytandiol amine [I] was prepared in the form of nutrient cosmetic liquid, of which composition is found in Table 6.

5 **Table 6**

Ingredients	Amount (wt%)
Phytandiol amine [I]	0.1
Glyceryl stearate	1.5
Stearyl alcohol	1.5
Lanoline	1.5
Polysorbate	1.3
Hardened plant oil	1.0
Mineral oil	5.0
Squalane	3.0
Trioctanoine	2.0
Dimethicone	0.8
Tocopheryl acetate	0.5
Carboxyvinyl polymer	0.12
Glycerine	5.0
1,3-butylene glycol	3.0
Sodium hyaluronate	5.0
Triethanol amine	0.12
preservative, perfume, colorant	Minute quantity
Distilled water	Residual quantity

**Formulation III**

Formulation III comprising the phytandiol amine [I] was prepared in the form of nutrient cream, of which composition is found in Table 7.

5 **Table 7**

Ingredients	Amount (wt%)
Phytandiol amine [I]	0.1
Lipophilic monostearyl glycerine	2.0
Stearyl alcohol	2.2
Stearic acid	1.5
Wax	1.0
Polysorbate 60	1.5
Sorbitan stearate	0.6
Hardened plant oil	1.0
Squalane	3.0
Mineral oil	5.0
Trioctanoine	5.0
Dimethicone	1.0
Sodium magnesium silicate	0.1
Glycerine	5.0
Betaine	3.0
Triethanol amine	1.0
Sodium hyaluronate	4.0
Preservative, perfume, colorant	Minute quantity
Distilled water	Residual quantity

**Formulation IV**

Formulation IV comprising the phytandiol amine [I] was prepared in the form of massage cream, of which



composition is found in Table 8.

**Table 8**

Ingredients	Amount (wt%)
Phytandiol amine [I]	0.1
Lipophilic monostearyl glycerine	1.5
Stearyl alcohol	1.5
Stearic acid	1.0
Polysorbate 60	1.5
Sorbitan stearate	0.6
Isostearylisostearate	5.0
Squalane	5.0
Mineral oil	35.0
Dimethicone	0.5
Hydroxyethyl cellulose	0.12
Glycerine	6.0
Triethanol amine	0.7
Preservative, perfume, colorant	Minute amount
Distilled water	Residual amount

#### **Formulation V**

- 5 Formulation V comprising the phytandiol amine [I] was prepared in the form of essence, of which composition is found in Table 9.

**Table 9**

Ingredients	Amount (wt%)
Phytandiol amine [I]	0.1
Glycerine	10.0
Betaine	5.0
PEG-1500	2.0
Allantoin	0.1

Table 9-continued	
Ingredients	Amount (wt%)
DL-panthenol	0.3
EDTA	0.02
Benzophenone-9	0.04
Hydroxyethylcellulose	0.1
Sodium hyaluronate	8.0
Carboxyvinyl polymer	0.2
Triethanol amine	0.18
Octyldodeces-16	0.4
Octyldodecanol	0.3
Ethanol	6.0
preservative, perfume, colorant	Minute amount
Distilled water	Residual amount

#### Formulation VI

Formulation VI comprising the phytandiol amine [I] was prepared in the form of facial pack, of which composition is found in Table 10.

Table 10

Ingredients	Amount (wt%)
Phytandiol amine [I]	1.0
Polyvinyl alcohol	15.0
Cellulose gum	0.15
Glycerine	3.0
PEG-1500	2.0
Cyclodextrine	0.15
DL-panthenol	0.4
Allantoin	0.1
Glyceryl ammonium	0.3
Nicotine amide	0.5

Table 10-continued	
Ingredients	Amount (wt%)
Ethanol	6.0
PEG-40 hardened castor oil	0.3
Preservative, perfume, colorant	Minute amount
Distilled water	Residual amount

#### Formulation VII

Formulation VII comprising the phytandiol amine [I] was prepared in the form of soap, of which composition is found in Table 11.

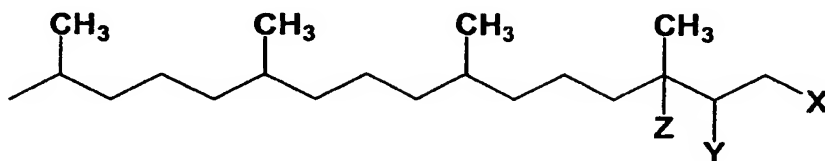
Table 11

Ingredients	Amount (wt%)
Palm oil fatty acid	1.5
Titania	0.5
Glycerine	0.5
EDTA-2Na	0.15
Perfume	0.7
Phytandiol amine [I]	0.5
Colorant	Adequate quantity
Soap chip base (water content, 15wt%)	To 100

Having described a preferred embodiment of the present invention, it is to be understood that variants and modifications thereof falling within the spirit of the invention may become apparent to those skilled in this art, and the scope of this invention is to be determined by appended claims and their equivalents.

What is claimed is:

1. A phytandiol amine derivative represented by the following formula (I):



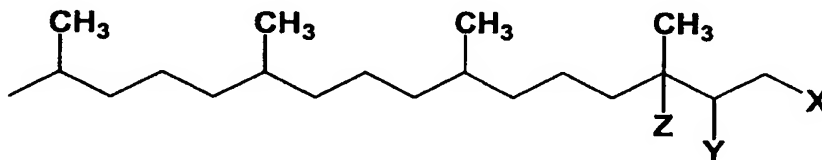
(I)

5 wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

10 2. A cosmetic composition for improving or alleviating acne, which comprises:

(a) a cosmetically effective amount of phytandiol amine derivative as active ingredient represented by the following formula (I); and

15 (b) a cosmetically acceptable carrier,



(I)

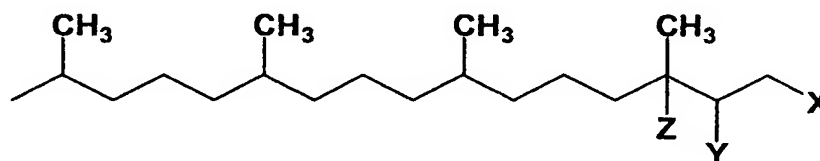
wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is

20 NH<sub>2</sub>.

3. A pharmaceutical composition for treating or preventing acne, which comprises:

(a) a pharmaceutically effective amount of phytandiol amine derivative as active ingredient represented by the following formula (I); and

(b) a pharmaceutically acceptable carrier,



(I)

wherein each of Y and Z is OH with the proviso that X is NH<sub>2</sub>, each of X and Z is OH with the proviso that Y is NH<sub>2</sub>, and each of X and Y is OH with the proviso that Z is NH<sub>2</sub>.

4. The composition according to claim 2 or 3, wherein the acne is selected from the group consisting of acne aggregata, bromide acne, common acne, conglobate acne, acne cosmetica, acne dtergicans, acne ephebica, acne fulminans, acne furunculoid, halogen acne, acne indurate, acne keloid, mechanical acne, acne medicamentosa, acne necrotica miliaris, acne neonatorum, acne oil, acne papulosa, pomade acne, premenstrual acne, acne rosacea, acne sycosiformis, tropical acne, acne venenata and acne vulgaris.

5. The composition according to claim 2 or 3, wherein the

phytandiol amine derivative is present in an amount of 0.01-20 wt% based on the total weight of the composition.

6. The composition according to claim 2, wherein the  
5 cosmetic composition is in the form of one selected from  
the group consisting of a solution, a suspension, an  
emulsion, a paste, an ointment, a gel, a cream, a lotion,  
a powder, a soap, a surfactant-containing cleanser, an oil,  
a powder foundation, an emulsion foundation, a wax  
10 foundation and a spray.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 01/01838

## CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: C07C 215/10; A61K 31/133

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>7</sup>: C07C 215/10; A61K 31/133

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN:Reg; STN:Cas

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0209158 A2 (KURARAY CO., LTD) 18 July 1986 (18.07.86) <i>page 54, example Nr. 6; claims.</i>	1-6

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

17 July 2002 (17.07.2002)

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 01/01838

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A1	9158	02-04-1980	AT	E	913	15-05-1982
EP	B1	9158	28-04-1982	DE	A1	2839973	03-04-1980
				DE	C0	2962632	09-06-1982



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